Granisetron extended-release (Sustol®) Abbreviated New Drug Update (ANDU)

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OVERVIEW[1]

- Sustol is an extended-release (ER) formulation of the serotonin (5-HT_3) antagonist, granisetron, that is indicated for the prevention of chemotherapy induced nausea and vomiting (CINV) in adults, specifically,: Approved in combination with other antiemetics in adults for the prevention of acute and delayed nausea and vomiting associated with initial and repeat courses of moderately emetogenic chemotherapy (MEC) or anthracycline and cyclophosphamide (AC) combination chemotherapy regimens.
- Contraindications/Warnings
  - ❒ Contraindication: hypersensitivity to granisetron, other components of the product, or any other $5HT_3$-antagonist.
  - ❒ Warnings: risk for hypersensitivity; gastrointestinal (GI) disorders including constipation and ileus; serotonin syndrome (although potential exists when used alone, there is a higher risk when used in combination with other serotonergic drugs); and injection sight reactions (including but not limited to infection, bleeding, pain, nodules, swelling and induaration)
- Availability
  - ❒ 10 mg/0.4 mL ER injection in a single-dosed, pre-filled syringe
- Dosage and Administration
  - ❒ Recommended dose in adults is 10 mg as a single subcutaneous (SC) injection 30 minutes prior to the emetogenic chemotherapy, on day 1.
  - ❒ Administer in combination with dexamethasone
  - ❒ Due to the viscosity of the solution, injection should be administered over 20-30 seconds
  - ❒ To be administered by a healthcare professional only
  - ❒ Do NOT administer more frequently than once every 7 days (effects last for 5 days)
  - ❒ Use for greater than 6 months is not recommended
- Adverse events
  - ❒ Most common adverse reactions (>3%): injection-site-reactions, constipation, fatigue, headache, diarrhea, abdominal pain, insomnia, dyspepsia, dizziness, asthenia and GERD.
- Drug Interactions
  - ❒ Granisetron is metabolized by CYP1A1 and CYP3A4 enzymes of the hepatic cytochrome P-450 system. Inducers or inhibitors of these enzymes can affect the clearance and/or half-life of this drug. Granisetron, itself, is neither an inducer nor inhibitor of the P-450 system.

- Serotonin syndrome has been described in patients who take 5-HT_3-antagonists with other serotonergic drugs like selective serotonin reuptake inhibitors (SSRIs) and serotonin and norepinephrine reuptake inhibitors (SNRIs), triptans, and monoamine oxidase inhibitors (MAOIs). Caution should be used when giving these drugs concomitantly.

- Pregnancy
  - Limited data for use during pregnancy are not sufficient to inform of drug-associated risks
- Renal Impairment
  - Avoid use in patients with severe impairment.
  - Do not administer more frequently than once every 14 days with moderate impairment
- Clinical Trials
  - Phase 3, randomized, multicenter, double-blind, parallel-group, non-inferiority study (n=733) compared a single 10 mg SC dose of granisetron ER (Sustol) to a single 0.25 mg intravenous (IV) dose of palonosetron HCl in cancer patients given MEC or AC chemotherapy. Patients also received oral and IV dexamethasone per treatment protocol.
    - Primary endpoints were percentage of patients with a complete response (CR) defined as no emetic episodes (vomit and/or retching) and no use of rescue medication during the acute phase (0-24hrs) and delayed phase (>24 hours to 120 hours).
    - Non-inferiority (defined as a lower level of difference of 15%) of granisetron ER to palonosetron HCl was demonstrated in the acute and delayed phases of MEC and of AC combination chemotherapy.
      - For MEC: 83% for granisetron ER versus 89% for palonosetron showed a CR in acute phase. Whereas, for delayed phase, 69% for granisetron ER versus 70% palonosetron was shown.
      - For AC: 70% for granisetron ER versus 64% for palonosetron showed a CR in acute phase. Whereas, for delayed phase, 85% for granisetron ER versus 74% for palonosetron was shown.

CLINICAL CONSIDERATIONS

- Granisetron ER injection (Sustol) offers a long-acting 5HT_3-antagonist anti-emetic agent used for CINV.
- Granisetron was first approved in 1993 and is now available generically as an oral tablet and injection.
- Also marketed in a transdermal patch formulation (Sancuso®).
- Currently, there is only one other long-acting 5HT_3-antagonist, IV palonosetron (Aloxi®), which has a similar length of efficacy (~5 days). Granisetron ER and palonosetron are both administered prior to emetogenic chemotherapy with the intent to prevent CINV.
- Not for use of acute or breakthrough CINV and not intended for use as a part of a repeat dosing multiday emetogenic chemotherapy regimen
- Used in combination with dexamethasone (with or without an NK1-antagonist)

SUGGESTED UTILIZATION MANAGEMENT

Anticipated Therapeutic Class Review (TCR) Placement	Antiemetic/Antivertigo Agents
Clinical Edit	Prior authorization will be required if product is determined to be non-preferred. Initial Criteria: • Patient must be at least 18 years of age; **AND** • Must be administered in combination with dexamethasone; **AND** o Patient is receiving highly emetogenic chemotherapy (HEC); **OR** o Patient has failed with another 5-HT_3 receptor antagonist (e.g. Zofran or Kytril) while receiving the current chemotherapy regimen; **AND** • Sustol is NOT covered for: o Breakthrough emesis; **OR** o Repeat dosing in multiday emetogenic chemotherapy regimens
Quantity Limit	10 mg per 7 days
Duration of Approval	Six months and may NOT be renewed
Drug to Disease Hard Edit	None

REFERENCES

1.Sustol [package insert]. Redwood City, CA; Heron Therapeutics; August 2016.
2.Referenced with permission from the NCCN Drugs & Biologics Compendium (NCCN Compendium®) Antiemesis. Version 2.2016. National Comprehensive Cancer Network, 2016. The NCCN Compendium® is a derivative work of the NCCN Guidelines®. NATIONAL COMPREHENSIVE CANCER NETWORK®, NCCN®, and NCCN GUIDELINES® are trademarks owned by the National Comprehensive Cancer Network, Inc." To view the most recent and complete version of the Compendium, go online to NCCN.org. Accessed August 2016.